II. AMENDMENTS TO THE CLAIMS

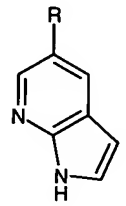
In the Claims

Please amend the following claims to conform to USPTO practice. No new matter is introduced with these amendments.

Listing of the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. A compound of formula (I) as defined below:



(I)

wherein:

R stands for carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein

the optionally substituted carbocyclyl or optionally substituted heterocyclyl group is optionally fused to an unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms,

each substitutable carbon atom in R, including the optional fused ring, is optionally and independently substituted by one or more of $C_{1\text{-}12}$ alkyl, $C_{2\text{-}12}$ alkenyl, carbocyclyl, or heterocyclyl, halogen, haloalkyl, OR^2, SR^2, NO_2, CN, NR^2R^2, NR^2COR^2, $NR^2CONR^2R^2$, NR^2COR^2, $NR^2CO_2R^2$, CO_2R^2, COR^2, $CONR^2R^2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$, wherein each R^2 may be the same or different and is as defined below and wherein:

the $C_{1\text{-}12}$ alkyl optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R^2)-, -S(O)- and –S(O_2)- wherein each R^2 may be the same or different and is as defined below;

the $C_{1\text{-}12}$ alkyl, carbocyclyl, or heterocyclyl group is optionally substituted by one or more of halogen, haloalkyl, OR^2, SR^2, NO_2, CN, NR^2R^2, NR^2COR^2, $NR^2CONR^2R^2$, NR^2COR^2, $NR^2CO_2R^2$, CO_2R^2, COR^2, $CONR^2{}_2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$; wherein each R^2 may be the same or different and is as defined below and

the carbocyclyl, or heterocyclyl group is optionally substituted by one or more C_{1-12} alkyl,

each saturated carbon in the optional fused ring is further optionally and independently substituted by =O, =S, $=NNHR^2$, NNR^2R^2, $=N\text{-}OR^2$, $=NNHCOR^2$, $=NNHCO_2R^2$, $=NNSO_2R^2$, or $=NR^2$, wherein each R^2 may be the same or different and is as defined below; and

each substitutable nitrogen atom in R is optionally substituted by R^3, COR^2, SO_2R^2 or CO_2R^2, wherein each R^2 and R^3 may be the same or different and is as defined below;

R^2 is hydrogen , C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4, SR^4, NO_2, CN, NR^4R^4, NR^4COR^4, $NR^4CONR^4R^4$, NR^4COR^4, $NR^4CO_2R^4$, CO_2R^4, COR^4, $CONR^4_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, SO_2 NR^4R^4, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, $-N(R^4)-$, -S(O)- and $-S(O_2)-$, wherein each R^4 may be the same or different and is as defined below;

R^3 is C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4, SR^4, NO_2, CN, NR^4R^4, NR^4COR^4, $NR^4CONR^4R^4$, NR^4COR^4, $NR^4CO_2R^4$, CO_2R^4, COR^4, $CONR^4_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, SO_2 NR^4R^4, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, $-N(R^4)-$, -S(O)- and $-S(O_2)-$, wherein each R^4 may be the same or different and is as defined below;

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl; with the proviso that when R is phenyl substituted with branched C_6-alkyl ($-CH(CH_2\text{-}CH(CH_3)(CH_3))\text{-}CH_2-$) incorporating two insertions –(CO)-and-NH-, the C_6-alkyl group is not substituted with –CN;

and the pharmaceutically acceptable salts, and other pharmaceutically acceptable biohydrolyzable derivatives thereof, ~~including~~ selected from the group comprising esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents ~~or~~ and prodrugs thereof.

2. A compound as claimed in claim 1, wherein R is an aryl or heteroaryl radical, optionally substituted with one or more of alkyl, haloalkyl, halogen, OR^8, S R^8, SO R^8, $(NR^8)_2$, wherein R^8 is independently selected from hydrogen, C_{1-4} alkyl or haloalkyl.

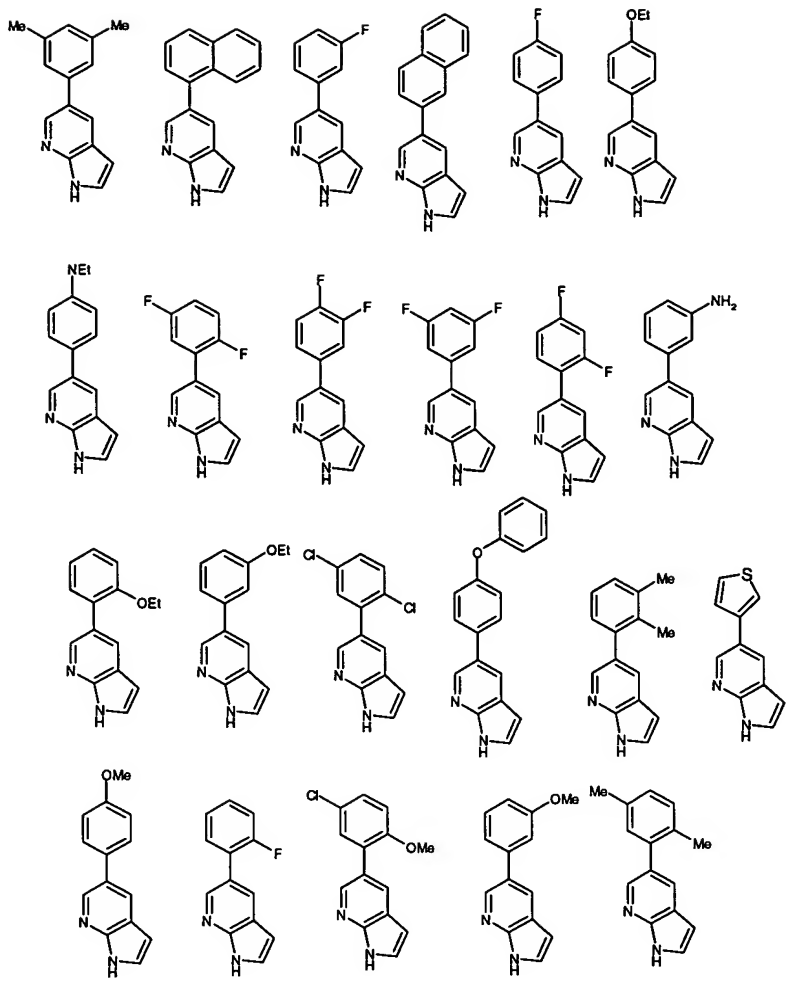
3. A compound as claimed in claim 1, wherein R is an optionally substituted aryl~~, preferably phenyl or napthyl~~.

4. A compound as claimed in claim 3, wherein R is phenyl substituted in the 4-(para) position.

5. A compound as claimed in ~~claim 3 or~~ claim 4, wherein R is phenyl substituted by NR^6R^6; and ~~where R^6 stands independently for H or C_{1-4} alkyl~~ wherein each R^6 is independently H or C_{1-4} alkyl.

6. A compound as claimed in claim 3 ~~or claim 4~~, wherein R is ~~substituted~~ aryl ~~and the substituent~~ substituted with is F, Cl, ~~or~~ Br, ~~preferably F~~; or haloalkyl, ~~preferably CF_3~~, or alkyl, ~~preferably methyl, ethyl or propyl~~.

7. A compound as claimed in claim 1, ~~which is one of the following~~wherein the compound is selected from the group consisting of:


Me
Me
F
OEt
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F
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F
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F
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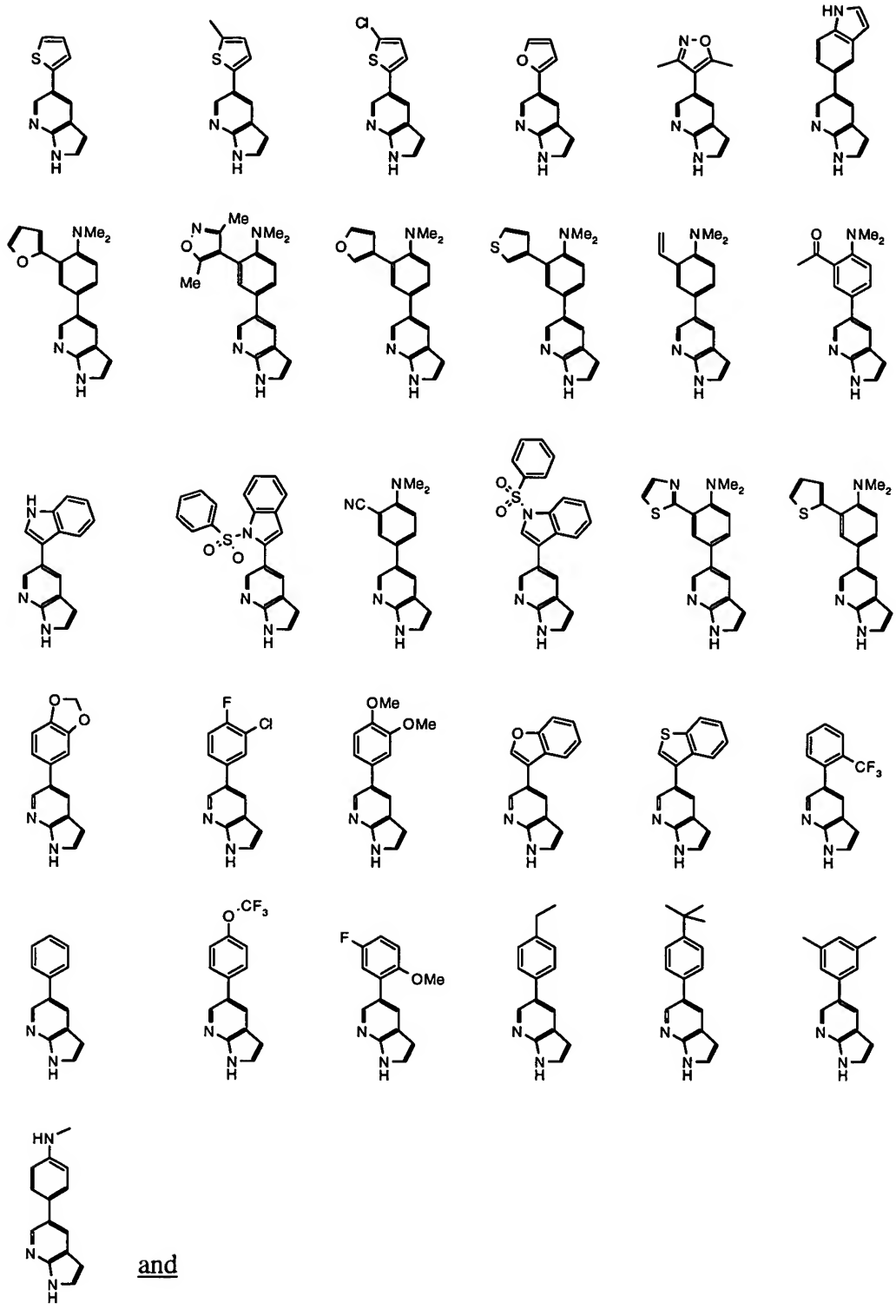
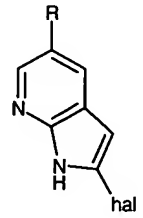


and

8. A prodrug of a compound as defined in ~~any of claims 1 to 7~~ claim 1.

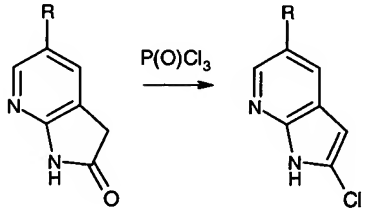
9. A process for the manufacture of ~~any one or more of~~ the compounds of ~~any one of claims 1 to 7~~ claim 1 which comprises hydrogenating a compound of the general formula (II):



(II)

~~in which~~wherein R is as defined in claim 1 and hal stands for a halogen atom, ~~e.g. using hydrogen and a catalyst such as Pd-C~~.

10. A process as claimed in claim 9, wherein the compound of the general formula (II) is made by halogenating a compound of the general formula (III) in the 2 position



(III) (II)

where R is as defined above and hal stands for halogen, ~~e.g. using $P(O)Cl_3$ at elevated temperature (about 100°C)~~.

11. A pharmaceutical formulation ~~composition~~ comprising a compound as defined in ~~any of claims 1 to 7~~ claim 1 ~~in combination with~~ and a pharmaceutically acceptable carrier, diluent or excipient.

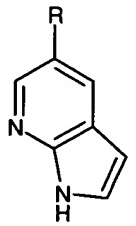
12. A pharmaceutical formulation ~~composition~~ as claimed in claim 11 further comprising one or more other active agent.

13. A pharmaceutical formulation ~~composition~~ as claimed in claim 11 wherein the composition further comprises an anti-inflammatory agent, ~~for example a p38 inhibitor~~.

14. (Canceled)

15. (Canceled)

16. A method for inhibiting JNK the method comprising administering to a subject in need thereof a pharmaceutical formulation comprising a compound of formula (I)



(I)

~~or a composition comprising a compound of formula (I), method for inhibiting JNK~~,
wherein:

R stands for carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein

the optionally substituted carbocyclyl or optionally substituted heterocyclyl group is optionally fused to an unsaturated, partially unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms,

each substitutable carbon atom in R, including the optional fused ring, is optionally and independently substituted by one or more of C_{1-12} alkyl, C_{2-12} alkenyl, carbocyclyl, or heterocyclyl, halogen, haloalkyl, OR^2, SR^2, NO_2, CN, NR^2R^2, NR^2COR^2, $NR^2CONR^2R^2$, NR^2COR^2, $NR^2CO_2R^2$, CO_2R^2, COR^2, $CONR^2R^2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$, wherein each R^2 may be the same or different and is as defined below and wherein:

the C_{1-12} alkyl optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R^2)-, -S(O)- and –S(O_2)- wherein each R^2 may be the same or different and is as defined below;

the C_{1-12} alkyl, carbocyclyl, or heterocyclyl group is optionally substituted by one or more of halogen, haloalkyl, OR^2, SR^2, NO_2, CN, NR^2R^2, NR^2COR^2, $NR^2CONR^2R^2$, NR^2COR^2, $NR^2CO_2R^2$, CO_2R^2, COR^2, $CONR^2_2$, $S(O)_2R^2$, $SONH_2$, $S(O)R^2$, $SO_2NR^2R^2$, $NR^2S(O)_2R^2$; wherein each R^2 may be the same or different and is as defined below and

the carbocyclyl, or heterocyclyl group is optionally substituted by one or more C_{1-12} alkyl,

each saturated carbon in the optional fused ring is further optionally and independently substituted by =O, =S, $=NNHR^2$, NNR^2R^2, $=N\text{-}OR^2$, $=NNHCOR^2$, $=NNHCO_2R^2$, $=NNSO_2R^2$, or $=NR^2$, wherein each R^2 may be the same or different and is as defined below; and

each substitutable nitrogen atom in R is optionally substituted by R^3, COR^2, SO_2R^2 or CO_2R^2, wherein each R^2 and R^3 may be the same or different and is as defined below;

R^2 is hydrogen, C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4, SR^4, NO_2, CN, NR^4R^4, NR^4COR^4, $NR^4CONR^4R^4$, NR^4COR^4, $NR^4CO_2R^4$, CO_2R^4, COR^4, $CONR^4_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, $SO_2\ NR^4R^4$, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, $-N(R^4)-$, -S(O)- and $-S(O_2)-$, wherein each R^4 may be the same or different and is as defined below;

R^3 is C_{1-12} alkyl or aryl, optionally substituted by one or more of C_{1-4} alkyl, halogen, C_{1-4} haloalkyl, OR^4, SR^4, NO_2, CN, NR^4R^4, NR^4COR^4, $NR^4CONR^4R^4$, NR^4COR^4, $NR^4CO_2R^4$, CO_2R^4, COR^4, $CONR^4_2$, $S(O)_2R^4$, $SONH_2$, $S(O)R^4$, $SO_2\ NR^4R^4$, $NR^4S(O)_2R^4$, wherein the C_{1-12} alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, $-N(R^4)-$, -S(O)- and $-S(O_2)-$, wherein each R^4 may be the same or different and is as defined below;

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

and the pharmaceutically acceptable salts, and other pharmaceutically acceptable biohydrolyzable derivatives thereof, ~~including~~ selected from the group comprising esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents ~~or~~ and prodrugs thereof.

17. ~~A compound or a composition as defined in claim 16, for selectively inhibiting~~ The method of claim 16, wherein JNK is JNK3.

18. ~~A compound or a composition as defined in claim 16, for use in the~~ A method for the prevention or treatment of a JNK-mediated disorder, the method comprising administering to a subject in need thereof the pharmaceutical formulation of claim 11.

19. ~~A compound or a composition as claimed in~~ The method of claim 18, wherein the disorder is a neurodegenerative disorder ~~(including dementia)~~, an inflammatory disease, a disorder linked to apoptosis, ~~particularly~~ neuronal apoptosis, an autoimmune disease, destructive bone disorder, proliferative disorder, cancer, infectious disease, allergy, ischemia reperfusion injury, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin induced platelet aggregation and/or ~~any~~ a condition associated with prostaglandin endoperoxidase synthase-2.

20. ~~A compound or composition as claimed in~~ The method of claim 19, wherein the neurodegenerative disorder ~~results from~~ is linked to apoptosis and/or is an inflammatory disease ~~inflammation~~.

21. ~~A compound or composition as claimed in claim 19 or claim 20~~, The method of claim 18, wherein the neurodegenerative disorder is: dementia; Alzheimer's disease; Parkinson's disease; Amyotrophic Lateral Sclerosis; Huntington's disease; senile chorea; Sydenham's chorea; hypoglycemia; head and spinal cord trauma, ~~including~~ traumatic head injury; acute pain, ~~and~~ chronic pain; epilepsy, ~~and~~ seizures; olivopontocerebellar dementia; neuronal cell death; hypoxia-related neurodegeneration; acute hypoxia; glutamate toxicity, ~~including~~ glutamate neurotoxicity; cerebral ischemia; dementia linked to meningitis, and/or dementia linked to neurosis; cerebrovascular dementia; or dementia in an HIV-infected patient.

22. ~~A compound or composition as claimed in claim 19 or 20~~, The method of claim 18, wherein the neurodegenerative disorder is a peripheral neuropathy, ~~including~~ mononeuropathy,

multiple mononeuropathy, ~~or~~ polyneuropathy, ~~such as may be found in diabetes mellitus~~, Lyme disease, ~~or~~ uremia; peripheral neuropathy caused by a toxic agent; a demyelinating disease, ~~such as~~ acute inflammatory polyneuropathy, ~~or~~ chronic inflammatory polyneuropathy, leukodystrophies, ~~or~~ Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder ~~(e.g. polyarteritis nodosa, SLE, Sjögren's syndrome)~~; multiple mononeuropathy secondary to sarcoidosis; multiple mononeuropathy secondary to a metabolic disease ~~(e.g. diabetes or amyloidosis)~~; or multiple mononeuropathy secondary to an infectious disease ~~(e.g. Lyme disease or HIV infection)~~.

23. ~~A compound or composition as claimed in~~The method of claim 18, wherein the disorder is inflammatory bowel disorder; bronchitis; asthma; acute pancreatitis; chronic pancreatitis; allergies of ~~various types~~; Alzheimer's disease; autoimmune disease, ~~such as~~ rheumatoid arthritis, systemic lupus erythematosus, glumerulonephritis, scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes, autoimmune haemolytis anaemia, autoimmune neutropaenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, ulcerative colitis, Crohn's disease, psoriasis, or graft vs host disease.

24. (Canceled)

25. (Canceled)

26. (Canceled)

27. (Canceled)

28. (Canceled)

29. (Canceled)

30. (Canceled)

31. A method as claimed in ~~any of claims 24-30,~~ claim 18, wherein one or more other active agent is administered to the individual simultaneously, subsequently, or sequentially to administering the compound.

32. A method as claimed in claim 31, wherein the other active agent is an anti-inflammatory agent such as a p38 inhibitor.

33. (Canceled)

34. (Canceled)

35. (Canceled)

36. (Canceled)

37. (Canceled)

38. (Canceled)

39. (Canceled)

40. (Canceled)

41. An assay for determining the activity of the compounds as defined in claim 1, ~~any of claims 1-7~~, comprising providing a system for assaying the activity and assaying the activity of a compound as defined in claim 1 ~~any of claims 1-7~~.

42. An assay as claimed in claim 41, wherein the assay is for the JNK inhibiting activity of the compound. ~~preferably for the JNK3-specific inhibiting activity of the compound~~.

43. An assay as claimed in claim 41 ~~or 42~~, wherein the assay is a Scintillation Proximity Assay (SPA) using radiolabelled ATP, or is ELISA.

44. (Canceled)

45. A method as claimed in claim 44, which is performed in a research model.

46. A method as claimed in claim 45, wherein the research model is an animal model.

47. (New) The compound of claim 3, wherein R is selected from the group consisting of phenyl and napthyl.

48. (New) The compound of claim 6, wherein R is aryl substituted with fluorine.

49. (New) The compound of claim 6, wherein the haloalkyl is CF_3.

50. (New) The compound of claim 6, wherein the alkyl is selected from the group consisting of methyl, ethyl, and propyl.

51. (New) The pharmaceutical formulation of claim 13, wherein the anti-inflammatory agent is a $_p$38 inhibitor.

52. (New) The assay of claim 41, wherein the assay is for the JNK3 specific inhibiting activity of the comound.

III. CONCLUSION

Applicants respectfully request that the pending claims 1-23, 31-32, 41-43, and 45-52 be examined in the instant application.

Respectfully submitted,

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